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Abstract: AIMS The SMART CRT study will assess the efficacy of an atrioventricular optimization algorithm to improve reverse remodeling among patients undergoing cardiac resynchronization therapy (CRT) in the presence of interventricular electrical delay. METHODS AND RESULTS The SMART CRT study is a global, multicenter, prospective, randomized study of patients undergoing CRT implantation. The primary endpoint of this trial is response rate to CRT, defined as decrease in left ventricular end-systolic volume (LVESV) 15% at 6 months compared to preimplant baseline. Additional prespecified analyses are: (1) clinical composite endpoint combining all-cause mortality, heart failure events, New York Heart Association class, and Quality of Life (using a patient global assessment instrument); (2) the individual components of the clinical composite endpoint; (3) 6-minute walk distance; (4) Kansas City Cardiomyopathy Questionnaire; (5) LVESV as a continuous variable; and (6) absolute left-ventricular ejection fraction. Subjects with intraventricular delay 70 ms measured between the right ventricular and left ventricular pacing leads will be randomized in a 1:1 ratio to have either an AV Delay and pacing chamber determined by SmartDelay™ or a Fixed AV Delay of 120 ms with biventricular pacing. Enrollment of an estimated 726 of subjects from up to 100 centers worldwide is planned to achieve 436 randomized subjects and 370 complete data sets required to power the primary endpoint. CONCLUSIONS This trial will provide important data regarding the importance of AV Delay programming in patients with prolonged interventricular delay at the pacing sites.

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The Rationale and Design of the SMART CRT Trial

Short Title: SMART CRT Study Design

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Abstract:

Aims: The SMART CRT study will assess the efficacy of an AV optimization algorithm to improve reverse remodeling among patients undergoing cardiac resynchronization therapy in the presence of interventricular electrical delay.

Methods and Results: The SMART CRT study is a global, multi-center, prospective, randomized study of patients undergoing cardiac resynchronization therapy (CRT) implantation. The primary endpoint of this trial is response rate to CRT, defined as decrease in left ventricular end systolic volume (LVESV) ≥ 15% at 6 months compared to pre-implant baseline. Additional prespecified analyses are: a) clinical composite endpoint combining all-cause mortality, heart failure events, NYHA class and Quality of Life (using a patient global assessment instrument), b) the individual components of the clinical composite endpoint, c) 6-minute walk distance, d) Kansas City Cardiomyopathy Questionnaire e) LVESV as a continuous variable, and f) absolute left-ventricular ejection fraction (LVEF). Subjects with intraventricular delay ≥ 70 msec measured between the right ventricular and left ventricular pacing leads will be randomized in a 1:1 ratio to have either an AV Delay and pacing chamber determined by SmartDelay™ or a Fixed AV Delay of 120 msec with biventricular pacing. Enrollment of an estimated 726 of subjects from up to 100 centers worldwide is planned to achieve 436 randomized subjects and 370 complete datasets required to power the primary endpoint.

Conclusions: This trial will provide important data regarding the importance of AV Delay programming in patients with prolonged interventricular delay at the pacing sites.

ClinicalTrials.gov Identifier: NCT03089281

Key words: Heart Failure; Cardiac Resynchronization Therapy; Clinical Trials;

Abbreviations:

AVO – Atrio-ventricular optimization

BSC – Boston Scientific Corporation

CRT – Cardiac resynchronization therapy

ECG – Electrocardiogram

HF – Heart failure

KCCQ – Kansas City Cardiomyopathy Questionnaire

LV – Left ventricular

LVEF – Left ventricular ejection fraction

LVESV – Left ventricular end systolic volume

NYHA – New York Heart Association classification.

Introduction

Cardiac resynchronization therapy (CRT) is a well-established treatment for patients with symptomatic heart failure (HF), a reduced left ventricular (LV) ejection fraction (LVEF) and QRS prolongation. CRT has a number of beneficial effects including improvement in measures of quality of life, reverse LV remodeling and reductions in HF hospitalizations and mortality.[1–5] The magnitude of benefit with CRT is affected by patient characteristics such as QRS duration and morphology, etiology of HF and gender. More recently it has been shown that procedural factors, such as LV pacing at sites of late electrical activation, as assessed by either the QLV or RV-LV durations, are associated with improved CRT response.[6–11]

Optimizing atrio-ventricular (AV) timing was a standard part of CRT management for many years, but routine AV optimization (AVO) is no longer recommended based on disappointing results from multicenter randomized trials.[12–14] However, retrospective analyses have shown that certain subgroups of patients may benefit from AVO, including those paced at sites of increased electrical delay.[15] To understand better the role of AVO among such patients, the SMART CRT study was designed as a prospective, randomized trial among patients paced with prolonged interventricular delay.

Rationale

A post hoc analysis of the SMART-AV trial showed that increasing RV-LV duration was associated with greater reverse remodeling with AVO compared with nominal programming.[11] For the analysis, the patient population was assessed by grouping into quartiles based on RV-LV duration. To provide more granularity to the data for the design of SMART CRT the splitting variable was changed to 10 msec increments. As shown in Panel A of Figure 1, the proportion of patients with an RV-LV duration greater than a given cutoff value diminishes as the RV-LV duration increases (median duration was 70 msec). The patient population was evaluated in a similar fashion in which the

response rates for AVO and nominal programming were compared. As the RV-LV duration increases, the difference in response rates also increases (Panel B of Figure 1). The curve is nonlinear with a plateau area. Choosing a large cutoff value increases the effect size but also diminishes the number of available patients. To maximize the proportion of patients who may benefit from AVO, enrolling patients with an RV-LV duration near the onset of the plateau region (70 msec) was chosen. This value ensures that a clinically meaningful improvement in response rate would be observed while ensuring that the cutoff value is applicable to the majority of patients.

Study Hypotheses

The primary hypothesis of SMART CRT is that among patients with prolonged inrerventricular delay between the RV and LV leads, CRT with AVO will result in greater reverse LV remodeling compared with CRT programmed at nominal settings.

Study Design

The SMART CRT study is a global, multi-center, prospective, randomized study that will enroll subjects who intend to undergo *de novo* implantation of a CRT System (Boston Scientific, Marlborough, MA) or upgrade from a preexisting single or dual chamber device. Only patients with at least one RV-LV duration $\geq$ 70 msec between programmable RV lead and LV pacing configuration, as measured automatically from the pulse generator, will be randomized. An acceptable pacing configuration is one with a pacing threshold $\leq$ 4.5 V at a pulse width of 0.5 msec and no diaphragmatic stimulation within 3 V above the pacing threshold. If multiple vectors meet the acceptable pacing criteria, the investigator will select a vector with an RV-LV delay within 10 msec

of the longest measured delay. In cases where there is no acceptable pacing configuation that meets randomization, the right or left ventricular lead can be repositioned at the discretion of the implanting physican; otherwise, the patient will be exited from the protocol. Subjects will be randomized in a 1:1 ratio to have either an AV Delay and pacing chamber determined by SmartDelay™ or a Fixed AV Delay of 120 msec with biventricular pacing. Of note, multisite pacing is not allowed in the protocol. Randomized subjects will be followed semi-annually for a minimum of 540 days ± 60 days window (i.e., 18 months) post implant. Figure 2 is a flow chart which describes the proposed study plan from first enrollment to study closure. All subjects will receive a *de novo* quadripolar Boston Scientific Cardiac Resynchronization Therapy Defibrillator (CRT-D) in conjunction with an ACUITY X4 LV lead. Lead locations will be at the discretion of the implanting physician.

Study Population

The study population consists of patients with a CRT indication scheduled for either *de novo* implantation or upgrade from single or dual chamber device to a CRT-D. Of note, given that multiple geographies were included in this trial it was decided to use as uniform as possible an inclusion criteria rather than indidiual guidelines of the various regions.

The inclusion and exclusion criteria are further described in detail within Tables 1 and 2, respectively.

Study Endpoints

The primary endopoint of this trial is proportion of patients with a positive response to CRT. CRT response is defined as a decrease in left ventricular end systolic volume (LVESV) ≥ 15% at 6 months compared to pre-implant baseline. The proportion of patients responding to CRT will be compared between the randomized groups. In addition to the formal endpoint hypotheses, comparisons between groups for pre-specified analyses include, but are not limited to: a) clinical

composite endpoint combining all-cause mortality, heart failure events, NYHA class and Quality of Life (using a patient global assessment instrument), b) the individual components of the clinical composite endpoint, c) 6-minute walk distance, d) Kansas City Cardiomyopathy Questionnaire (KCCQ), e) LVESV as a continuous variable, and f) LVEF.

Trial Oversight

The study protocol was developed with a steering committee consisting of 8 physicians and a patient advocate. The local ethics committees of all participating sites are required to approve the study protocol. Central and onsite monitoring, data review and safety oversight will be provided by the sponsor, Boston Scientific (Marlborough, MA, USA). Echocardiograms will be interpreted by a blinded core laboratory. All heart failure events and deaths will be reviewed by an independent clinical event committee.

Power Calculations

For the primary endpoint difference in response rates between the group with a fixed AV Delay (120ms) and AV Delay as specified by SmartDelay the sample size is powered to obtain a 90% confidence level with a one-sided alpha of 2.5%. It is expected that 60% of enrolled patients will have an RV-LV-interval of ≥ 70 msec and undergo randomization. Attrition after randomization is expected to be 15%. Under those assumptions, an estimated 726 subjects will be enrolled to achieve 436 randomized subjects and 370 patients in the analysis cohort.

Statistical Analyses

The Primary Endpoint, in addition to the additional analyses, will be evaluated using intention-to-treat methodology, in which subjects with complete datasets are evaluated according to their randomized treatment groups. The Primary Endpoint will be evaluated using a chi-square test with a one-sided significance level of 2.5%, comparing the proportion of responders in the SmartDelay randomized group to the Fixed AV Delay randomized group. The following sensitivity analyses for the Primary Endpoint will be performed: intention-to-treat with missing endpoint data imputed via multiple imputation, on-treatment in which subjects are analyzed according treatment received and per protocol including only subjects programmed to their randomized assignment are included.

The clinical composite endpoint will be assessed utilizing a Cochran-Armitage test for trend. Cochran–Mantel–Haenszel tests will be used to evaluate NYHA classification and patient global assessment. The continuous outcomes of 6-minute walk distance, KCCQ, LVESV and LVEF will be tested using a two-sample t-test. The time-to-event analyses of all-cause mortality and heart failure events will be evaluated using a log-rank test; data from any subjects who are event-free will be right censored on the final date of study participation.

Subgroup analyses for the Primary Endpoint will be performed by testing the interaction between the subgroup and randomized group utilizing a logistic regression model. Subgroup analyses will be performed on the following characteristics: age, gender, ischemic etiology, conduction disorder, QRS duration, LV lead location, baseline NYHA classification and SmartDelay recommended programming (LV only vs. biventricular pacing, and AV Delay equal to 120±20 msec vs. all others). Multivariable logistic regression modeling will also be performed using these characteristics.

An interim sample size re-estimation will be performed after at least half of the required 6 month datasets (N = 185) have been completed and reviewed by the core lab. The pooled and blinded response rate across both groups will be assessed in this interim sample size re-assessment cohort.

The observed rate will be weighted by the number of patients in each group and compared to the assumed weighted rate. If the observed rate is less than the assumed rate, the number of patients required for randomization will be increased accordingly, up to a maximum of 456 randomized subjects. The treatment effect will not be calculated, thereby maintaining the blind.

Discussion

Despite early enthusiasm for AV optimization, primarily using echocardiographic techniques, current consensus documents and guidelines do not recommend routine optimization based on the results of prospective, multicenter trials.[16,17] As such, routine AVO has fallen out of favor. However, analyses of the SMART-AV trial showed that the electrogram based algorithm (SmartDelay) was more effective among patients with the LV lead at sites with a long left ventricular (i.e. QLV)[15]or interventricular (RV-LV) delay.[11] The present trial is designed to confirm these findings prospectively by only randomizing patients with a prolonged RV-LV duration at implant. This would support the hypothesis that AVO is most effective among patients more likely to respond to CRT rather than the initial hope of AVO to "convert" non-responders to responders.

The Adaptive CRT trial was another randomized trial which showed no benefit of AVO for the whole CRT cohort,[13] but a subgroup was identified with LBBB and normal PR interval that was associated with an improved response.[18] The AdaptResponse trial is a prospective study designed to validate this finding..[19] There are some similarities between these algorithms as both are designed to promote fusion of intrinsic conduction to produce more synchronous LV activation including LV only pacing rather than choosing AV delays to optimize LV filling. Since LBBB patients have longer RV-LV times,[10] SMART CRT and AdaptResponse may evaluate a common mechanistic hypothesis that AVO that promotes electrical resynchronization is of value primarily among patients with electrical delay.

There has been much interest in reducing the purported non-responder rate to CRT. Although there is no consensus on the definition of response to this therapy it is clear that optimizing outcomes is an important goal. In this regard, certain clinical factors such as etiology of HF, gender and ECG characteristics including QRS duration and morphology affect CRT response. More recently, the role of targeting LV pacing to areas of late mechanical or electrical delay has also been shown to impact CRT response. The SMART CRT trial will further add to our understanding of strategies to optimize CRT outcomes if the results show a benefit of combining AVO with pacing at site of prolonged interventricular conduction delay.

In summary, SMART CRT is a prospective, randomized study that will be the first trial to evaluate the SmartDelay algorithm in patients with interventricular conduction delay using a quadripolar left ventricular transvenous lead. At present there are no multicenter, randomized, blinded trials showing the benefit of AVO for CRT so this study will potentially establish the benefit of routine AVO in a subset of CRT patients.

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Author Contributions:

Dr. Gold: concept/study design, critical revision and drafting the article

Dr. Auricchio: concept/study design, critical revision of the article

Dr. Leclercq: concept/study design, critical revision of the article

Dr. Lowy: concept/study design, critical revision of the article

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Mr. Yong: concept/study design, critical revision of the article

Mr. Wold: concept/study design, critical revision of the article

Dr. Ellenbogen: concept/study design, critical revision of the article

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Figure Legends

Figure 1: Justification for Interventricular Delay Cut-off

Panel A) Percent of CRT population with delay greater than RV-LV cutoffs, the median value was 70 msec.

Panel B) The difference in CRT response between the patients in the SmartDelay and the Fixed delay (at 120ms) cohorts by RV-LV cutoff. Cutoffs represent RV-LV durations equal to or longer than the specified cutoff value.

Data obtained from the SMART-AV Trial.

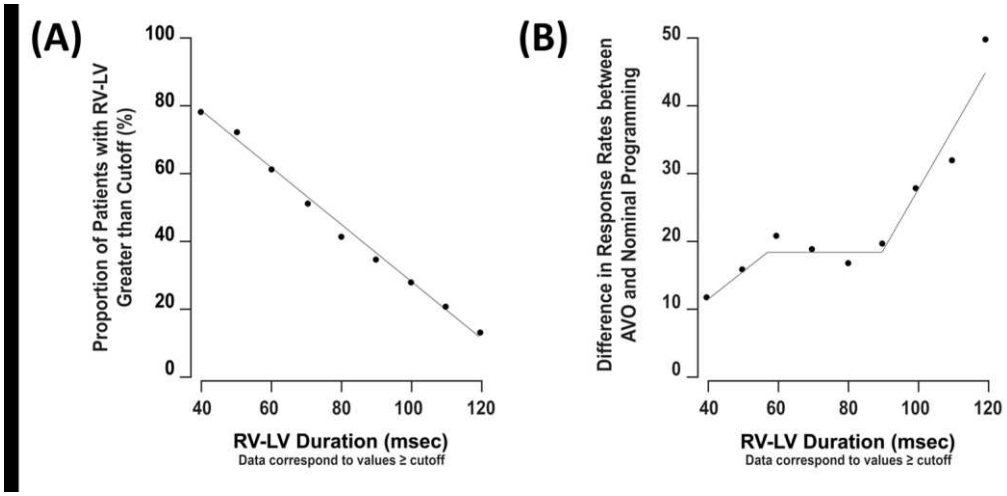

Figure 2: Study Design Flow Chart

Eligible patients (RV-LV duration ≥ 70 msec) will be randomized in the post-implant period. Response rates (proportion of patients with ≥ 15% decrease in LVESV from pre-implant echocardiogram) as well as Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-Minute Hall Walk (6MW), LVESV and LVEF will be evaluated at a 6-month follow-up.

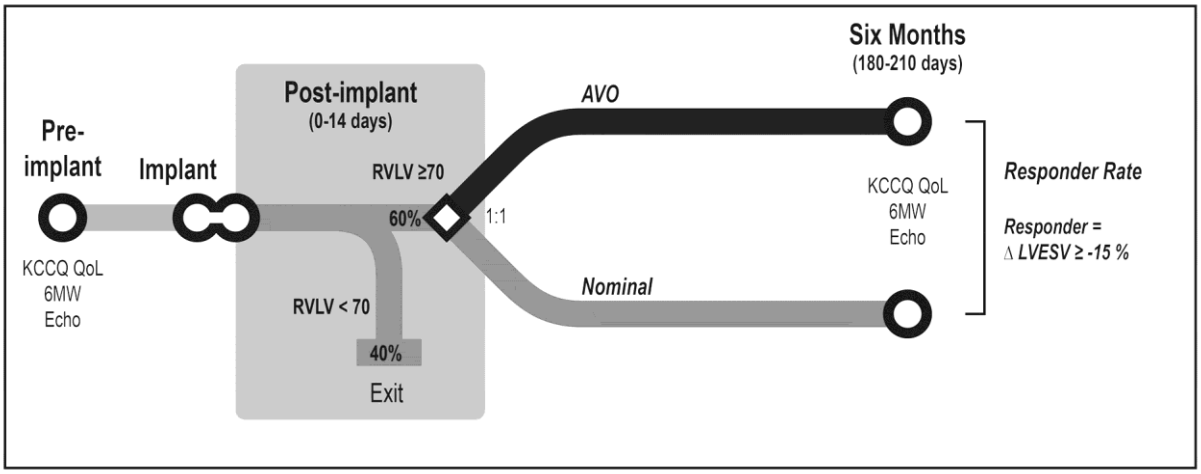

Table 1: Study inclusion criteria

Qualifying subjects are those with heart failure who CRT indications defined as those subjects who receive stable optimal pharmacologic therapy for heart failure and who meet any one of the following classifications:
• **Moderate to severe heart failure (NYHA Class III-IV) with LVEF ≤ 35% and QRS duration ≥ 120 msec**
• **Mild heart failure (NYHA Class II) with LVEF ≤ 30% and LBBB with QRS duration ≥ 130 msec** This indication is modified in Japan to restrict the QRS cutoff to 150 msec
• **Asymptomatic heart failure (NYHA Class I) with ischemic cardiomyopathy, LVEF ≤ 30% and LBBB with QRS duration ≥ 130 msec** This indication is eliminated in Japan
Subject is age 18 years old or above, or of legal age and willing and capable to give informed consent specific to each country and national laws
Subject must be indicated for a CRT-D system implant. This includes subjects who are indicated to receive an upgrade to a BSC quadripolar CRT-D device from a previously implanted device

Subject is willing and capable of complying with visits and procedures as defined by this protocol

CRT=cardiac resynchronization therapy, LBBB=left ventricular bundle branch block, LVEF=left ventricular ejection fraction

Table 2: Study exclusion criteria

Subjects with documented permanent complete AV block
Subjects with permanent or chronic AF or in AF at the time of enrollment
Subjects who have previously received cardiac resynchronization therapy with pacing in the left ventricle
Subjects on the active heart transplant list or who has or is to receive a VAD
Life expectancy shorter than 12 months due to any medical condition (e.g., cancer, uremia, liver failure)
Subject with a known or suspected sensitivity to dexamethasone acetate
Women of childbearing potential who are or plan to become pregnant during the course of the trial
Subjects currently requiring dialysis

AF=atrial fibrillation, AV=atrioventricular**, VAD=ventricular assist device**